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ABSTRACT

Nuclear factor-kappaB (NF-κB) plays an important role in regulating the expression of a variety of rapid response genes involved in the coordinated response to inflammation, injury and sepsis. The inducible nitric oxide synthase (iNOS) is primarily regulated by transcriptional mechanisms and activation of NF-κB by pro-inflammatory mediators (e.g. LPS) plays a pivotal role in the process. We have investigated NF-κB activation by LPS in Kupffer cells of LPS tolerant and non-tolerant male and female rats. In addition we have studied the modulation of hepatic nitric oxide production by LPS tolerance and ethanol, and the gender dependence of redox balance (as assessed by GSH and GSSG assay) in Kupffer cells of LPS tolerant rats. Finally we have also studied sexual dimorphism of gene expression pursuant to NF-κB activation, in cross-tolerance between acute ethanol and LPS. Gender dependent modulation of iNOS mRNA and COX-2 mRNA expression by LPS and ethanol was shown in liver cells. The results of all of these studies, as documented by the attached full paper and 4 abstracts demonstrate that the better maintained redox balance in Kupffer cells of tolerant female rats , the differences in the LPS-tolerance-induced alteration in the ethanol effect on nitric oxide production may have significance as a protective mechanism in females against potential oxidative cell injury.

FINAL REPORT

GRANT #: N00014-98-1-0460

PRINCIPAL INVESTIGATOR: Judy A. Spitzer, Ph.D.

INSTITUTION: LSU Health Sciences Center

GRANT TITLE: Gender Difference in Immune Defense Mechanisms: Potential application to the management of combat associated major trauma

AWARD PERIOD: 1 October 1998 - 31 December 2000

OBJECTIVES: To delineate some of the gender-related influences on NF-κB-mediated immediate responses to traumatic injuries that may well occur in a combat associated setting; to test the hypothesis that therapeutic responses to traumatic injury are modulated in a gender-dependent fashion both in the mediation of NF-κB activation and in the subsequent alteration in gene expression in relevant cells integrating host defense.

APPROACH: The basic approach involves parallel experiments in age-matched male and female rats subjected to identical treatments. This approach was to serve our ultimate goal to provide improved combat casualty care by identifying steps in the initial response to trauma and injury, that could be targeted for therapeutic interventions. Tests and evaluation included investigating NF-κB activation by LPS in Kupffer cells of LPS tolerant and non-tolerant rats. The modulation of hepatic nitric oxide production by LPS tolerance and ethanol, redox balance (as assessed by GSH and GSSG assay) in Kupffer cells of LPS tolerant rats. Finally, sexual dimorphism of gene expression was also studied in terms of iNOS mRNA and COX-2 mRNA expression as impacted by LPS and ethanol in liver cells.

ACCOMPLISHMENT: Our investigations have demonstrated the gender dependence of NF-κB activation by LPS and LPS tolerance in various liver cells as well as hepatic nitric oxide production and redox balance.

CONCLUSION: Sexual dimorphism plays a role in several hepatic immune defense mechanism such as LPS-induced NF-κB activation, nitric oxide production and subsequent alteration in appropriate gene expression. LPS tolerance, alone or combined with ethanol intoxication also modulates these parameters in a gender-dependent fashion.

SIGNIFICANCE: The results of our studies in male and female rats subjected to LPS treatment and/or ethanol intoxication revealed that the gender-related differences in these mechanisms are of potential significance as a protective measure in females against oxidative cell injury in the liver.

PUBLICATIONS AND ABSTRACTS:

1. Spitzer, J.A. and J.J. Spitzer (2000). LPS tolerance and ethanol modulate hepatic NO production in a gender dependent manner. Alcohol, 21: 27-36

2. Spitzer, J.A. and VandeStouwe (2000). LPS tolerance modulates redox balance and NF-kB activation in Kupffer cells in a gender dependent manner. 5th World Congress on Trauma, Shock, Inflammation and Sepsis. Feb. 29-March 4, Munich, Germany.

3. Spitzer, J.A., M. Zheng and J.J. Spitzer (2000). Gender dependent modulation of gene expression by LPS tolerance and ethanol in liver cells. FASEB J 14(8), A1358.

4. Spitzer, J.A. and M. Zheng (2000). Sexual dimorphism of gene expression in cross tolerance between acute ethanol and LPS treatment. Alcoholism: Clin. Exper. Res. 24(5). 131A.